

REMARKS

New claims 27 and 28 have been added. Upon entry of the amendment, claims 1, 3, 6-8, and 13-16, 18-23, 25-28 will be pending in this application. Reconsideration of the merits of this application is respectfully requested in light of the above amendment and the following remarks.

No new matter has been added as a result of the claim amendments. The antibody BM7 recited in new claims 27 and 28 was previously deleted from the claims and is now being reintroduced.

Objections

The Examiner maintained the objection to the amendment filed January 8, 2002 because it allegedly introduced new matter. Applicants asserted that support for the objected to claim language could be found in originally filed claim 1 of the PCT application, of which the present application is a national stage application. However, the Examiner maintained the objection, stating that the claim 1 of the PCT application is not drawn to any immunotoxin that is "directed to epitopes on a combination if these." Applicants respectfully traverse this objection.

Support for the objected to claim language can be found in claim 9 of the underlying PCT application. As such, the objected to language does not introduce new matter. Accordingly, Applicants assert that cancellation of the language objected to should not be required. A determination to this effect is earnestly solicited.

Rejection Under 35 USC 112, Second Paragraph

Claims 1, 3, 6-8, 20 and 25-26 have been rejected under 35 USC 112, second paragraph as allegedly being indefinite for reciting the term "active toxin fragment". Applicants respectfully traverse the rejection.

As stated in Applicants' Response mailed June 24, 2002, one of skill in the art would find the term "active toxin fragment" clear and definite in light of the specification. As the claimed method is directed to immunotoxins and their use to induce toxic effects in cells, one of skill in the art would understand that an active fragment of a toxin would be a fragment possessing toxic activity. In the case of *Pseudomonas* exotoxin A, which exerts its toxic effect through inhibition of protein synthesis, one skilled in the art would understand "active toxin fragment" to mean a fragment capable of inhibiting protein synthesis. A further discussion of active toxin fragments

can be found in the references provided in attachments 2-1 (Godal et al., *Int. J. Cancer*, 42, 400-404 (1988) and 2-2 (Godal et al. *Cancer Research*, 47, 6243-6247, 1987), which show that the language "active toxin fragment" was well understood in the art as far back as 1987.

Withdrawal of the rejection is respectfully requested.

Rejection Under 35 USC 112, First Paragraph

Claims 1, 6-8, 13-14, 20-23, and 25-26 have been rejected under 35 USC 112, first paragraph because the specification allegedly does not provide an enabling disclosure for a method of killing breast cancer cells or other carcinoma cells *in vivo* and *ex vivo* wherein the method comprises incubation with immunotoxins directed against an EGP2 antigen and a MUC1 antigen. Applicants respectfully traverse the rejection.

The Examiner appears to be stating that only the specific antibodies used in the immunotoxins described in the specification would be appropriate for rendering a synergistic effect against breast cancer cells. Specifically, the Examiner appears to be stating that the Apostolopoulos reference teaches that different epitopes of the MUC1 antigen are exposed in breast cancer cells. Accordingly, one would not be able to predict which antibodies that bind this antigen in normal cells would also be able to bind this antigen in tumor cells. Further, the Examiner cites the McClaughlin reference as teaching that the MOC31 antibody specifically localizes to EGP2 on tumor cells but does not localize to normal tissues.

Again, Applicants respectfully assert that the Examiner is clearly mischaracterizing the McClaughlin reference, as it clearly suggests that the reason why the antibody does not react with normal tissue *in vivo* is due to an issue of accessibility of the antibody to those normal cells. This reference does not suggest in any way that an epitope change has occurred rendering the antibody unable to bind normal cells. As stated in Applicants' Response to the previous Office Action, the McClaughlin reference is actually favorable to Applicants' position. That is, if an antibody directed to the MUC1 antibody were not accessible to normal cells, one would expect more selective killing of breast cancer cells.

As Applicants previously asserted the surprisingly good efficacy and low toxicity of the claimed method is likely due to increased expression the MUC1 and EPG2 antigens on tumor cells and increased rates of internalization of immunotoxin bound to these antigens, rather than a change in epitopes of these antigens in cancer cells. The Examiner has requested objective

EPG2

MUC-1

evidence in support of Applicants' hypothesis and demonstrating that MOC31 binds to normal cells. Responding to the Examiner's request, Applicants respectfully provide the at appendices 3-1 to 3-8 evidence that MOC 31, BM7 and BM2 bind normal cells. At Appendix 3-1, Applicants provide: Engerbraaten et al., *Int. J. Cancer*, 88, 970-976, 2000. This reference teaches that the antigen for the MOC31 antibody is present in epithelial cells in the digestive tract, including the gall ducts and the pancreatic gland and the kidneys and that the MOC31 antibody binds these antigens. See p. 975, first column. At Appendix 3-2: DeLeij et al., *Int. J. Cancer*, 8(supp.), 60-63, 1994 (first page) describes that the EGP2 antigen (GA 733-2) is expressed on normal cells. Appendix 3-3: Bergsagel et al., *J. Immunol.*, 148(2), 590-596, 1992 (first page) describes a murine homolog of EGP-2 is expressed on normal cells. A further reference regarding GA 733-2 is provided at Appendix 3-4: Szala et al., *Proc. Nat. Acad. Sci. USA*, 87, 3542-3546, 1990 (first page). A reference describing that KSA, represented by KS1/4, which is the same as EGP-2, is expressed on normal epithelial tissue is presented at Appendix 3-5: Strnad et al., *Cancer Research*, 49, 314-317, 1989. Notably, it is shown to be expressed on the apical side of the cell. In addition, imaging on patients with radioactivity labeled MOC 31 is documented in Appendix 3-8: Kisterink et al., *J. Nuclear Med.*, 36(12), 2356-2362, 1995. This reference teaches that MOC 31 is known to bind normal cells. See Figure 6 at p. 2361 and accompanying text at column 2, p. 2361. Some uptake of MOC 31 is temporarily taken up in some epithelial cells, but the antibody is highly concentrated in tumor tissue. This demonstrates the important differences in the level of expression and accessibility of the antigen in tumor and normal cells.

In addition, Applicants present at Appendices 3-6 and 3-7 descriptions of the reactivity of BM7 and BM2, respectively. These descriptions were received from Dr. Kaul and included in this application with permission to use the antibody clinically. While these documents are in German, it can be readily seen that BM7 and BM2 are reactive with normal cells.

In light of the above, Applicants respectfully assert that the surprising results achieved by the claimed method and the scope of the claimed method as it relates to immunotoxins to MUC1 and EGP2 for killing cancer cells is fully enabled. Table 1 of the specification provides evidence that a synergistic effect can be achieved when practicing the claimed method by using immunotoxins directed to MUC1 and EGP2 antigens. One skilled in the art would appreciate, in

light of the present specification, that immunotoxins other than those disclosed and which are directed to MUC1 and EGP2 antigens would be effective according to the claimed method.

Withdrawal of the rejection is respectfully requested.

The Examiner additionally stated that MOC 31 is available for research only and thus does not meet the requirement for a method of treatment. However, a MOC 31 immunotoxin according the present specification has been run through a Phase 1 study for acceptance as a medicament. A copy of the clinical protocol is enclosed at attachment 5. Thus, it is documented that the MOC 31 immunotoxin according to the claimed invention is used in a method for treatment.

Rejection Under 35 USC 112, First Paragraph

Claims 3, 15, 16, 18, and 19 have been rejected under 35 USC 112, first paragraph as allegedly lacking written description. Applicants traverse the rejection. The Examiner stated that the specification does not provide evidence that the antibody BM2 is known and readily available to the public, reproducible from a written description (e.g., sequenced), or deposited. Applicants maintain that BM2 is publicly available. However, to facilitate prosecution of the present claims, Applicant has begun the process to deposit the BM2 antibody with the ATCC under the terms of the Budapest Treaty. Applicants will file appropriate documentation regarding the deposit after the deposit is made. Upon completion of the deposit and filing of appropriate documents, reconsideration of this rejection is respectfully requested.

With regard to new claims 27 and 28, which recite the antibody "BM7," Applicants have begun the deposit process for hybridomas producing such antibody.

Rejection Under 35 USC 112, Second Paragraph

Claims 3, 15, 16, 18, and 19 have been rejected under 35 USC 112, second paragraph as allegedly being indefinite for recitation of the term "BM2". Applicants respectfully traverse the rejection. Applicants maintain that BM2 is a publicly available antibody and that one of skill in the art would know understand what is meant by BM2 in light of the specification. However, to facilitate prosecution of the present claims, a deposit of a hybridoma producing the BM2 antibody under the terms of the Budapest Treaty is currently underway. Upon completion of the

deposit and submission of appropriate documents regarding the deposit, Applicants will amend the specification to refer to the deposit accession number and will amend the claims accordingly as well. At such time, reconsideration of the merits of the claimed invention is respectfully requested.

With regard to new claims 27 and 28, which recite the antibody "BM7," Applicants have begun the deposit process for hybridomas producing such antibody.

Rejection under 35 USC 103

Claims 1, 13, 14, and 24 have been rejected under 35 USC 103 as allegedly being obvious for reasons previously set forth in Paper NO. 20, Section 9, pages 5-7. Applicants respectfully traverse the rejection.

The Examiner appears to be indicating that the unexpected synergy between BM7 and MOC 31 and BM2 and MOC 31 cannot be extended to different immunotoxins recognizing the MUC1 and EGP2 antigens.

As stated in Applicants' Response to the previous Office Action, the specification provides several exemplary instances of unexpected synergy between immunotoxins directed to the MUC1 and EGP2 antigens. Further, as stated above, one reason for the unexpected synergy may be the increased co-expression of these antigens on tumor cells relative to normal cells and in the increased internalization rate of immunotoxins in tumor cells. Upon reading the specification, one skilled in the art would reasonably expect that different immunotoxins directed to the same antigens would also produce the surprising and unexpected results shown by the inventors.

In light of the unexpected results and reasonable expectation of further similar results, withdrawal of the rejection is respectfully requested.

CONCLUSION

Applicants respectfully assert that the claims, upon entry of this amendment, are in a condition for allowance, and earnestly solicit a notice to that effect.

Applicants believe all of the outstanding objection and rejections have been addressed. If the Examiner has any questions regarding the foregoing, it is respectfully requested that she call the undersigned.

Respectfully Submitted,

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Enclosures:

- Appendix 2-1 (Godal et al., *Int. J. Cancer*, 42, 400-404, 1988);
- Appendix 2-2 (Godal et al. *Cancer Research*, 47, 6243-6247, 1987);
- Appendix 3-1 (Engerbraaten et al., *Int. J. Cancer*, 88, 970-976, 2000);
- Appendix 3-2 (DeLeij et al., *Int. J. Cancer*, 8(supp.), 60-63, 1994 (first page);
- Appendix 3-3 (Bergsagel et al., *J. Immunol.*, 148(2), 590-596, 1992 (first page));
- Appendix 3-4 (Szala et al., *Proc. Nat. Acad. Sci. USA*, 87, 3542-3546, 1990 (first page));
- Appendix 3-5 (Strnad et al., *Cancer Research*, 49, 314-317, 1989);
- Appendix 3-6 (description of the reactivity of BM7);
- Appendix 3-7 (description of the reactivity of BM2);
- Appendix 3-8 (Kisteriink et al., *J. Nuclear Med.*, 36(12), 2356-2362, 1995); and
- Appendix 5 (clinical protocol regarding MOC 31)

Claims pending after February 2003 Amendment

1. Method to kill breast cancer cells or other carcinoma cells expressing the same target antigens in a cell population selected from the group consisting of cells comprising nucleated cells in peripheral blood and bone marrow cells comprising CD-34⁺ cells selected from the above nucleated cells, the method comprising:
incubating the cell population with a combination of two or more immunotoxins, wherein each immunotoxin comprises a conjugate between an antibody or antigen binding antibody fragments and a cell toxin or active toxin fragments, or a recombinantly produced antibodies or antigen binding antibody fragments, and toxins or active toxin fragments, wherein the antibodies or antigen binding antibody fragments are directed to epitopes on the antigen EGP2 expressed by the gene GA733-2 and to epitopes on the antigen expressed by the MUC1 gene and the toxin is Pseudomonas exotoxin A.
3. The method according to claim 1, wherein the antibodies are MOC31 and BM2, or antigen binding fragments thereof.
6. The method according to claim 1 wherein said incubating consists of administering the immunotoxins in vivo.
7. The method according to claim 6, wherein the immunotoxins are administered systemically.
8. The method according to claim 6, wherein the immunotoxins are administered directly into a tumor or intrapleurally or intra-abdominally.
13. The method of claim 1, wherein said incubating consists of administering the immunotoxins *ex vivo*.

14. A method for killing breast cancer cells or other carcinoma cells expressing the same antigens in a cell population comprising nucleated peripheral blood cells or bone marrow cells, the method comprising

obtaining the population of cells that contains the breast cancer cells or other carcinoma cells expressing the same antigens;

contacting the population of cells *ex vivo* with two or more immunotoxins, wherein a first immunotoxin comprises a PE molecule conjugated to an antibody or an antibody fragment capable of binding an EGP2 antigen which is expressed by a GA733-2 gene and a second immunotoxin comprising a PE molecule conjugated to an antibody or an antibody fragment capable of binding an antigen encoded by the MUC1, MUC2, or MUC3 gene.

15. The method according to claim 14, wherein the first immunotoxin comprises a PE molecule conjugated to a MOC31 antibody or an antigen-binding antibody fragment thereof, and the second immunotoxin comprises a PE molecule conjugated to a BM2 antibody or an antigen-binding antibody fragment thereof.

16. The method according to claim 14, wherein the cell population is obtained from a cancer patient.

18. The method according to claim 14, wherein the cell population comprises CD34+ cells

19. The method according to claim 18, wherein the cell population is enriched or positively selected for CD34+ cells.

20. The method according to claim 1 wherein treatment of the cell population with the two or more immunotoxins causes relatively high toxicity to cancer or carcinoma cells and relatively low toxicity to CD34+ cells in the population.

21. A method for killing breast cancer cells or other carcinoma cells expressing the same antigens in a patient, the method comprising

administering to the patient a therapeutically effective amount of two or more immunotoxins, wherein a first immunotoxin comprises a PE molecule conjugated to an antibody or an antibody fragment capable of binding an EGP2 antigen which is expressed by a GA733-2 gene and a second immunotoxin comprises a PE molecule conjugated to an antibody or an antibody fragment capable of binding an antigen encoded by the MUC1, MUC2, or MUC3 genes.

22. The method according to claim 21, wherein the patient is a cancer patient.

23. The method according to claim 21, wherein the malignant cells are carcinomas.

25. The method according to claim 7, wherein the immunotoxins are administered systemically to kill malignant cells.

26. The method according to claim 25, wherein the malignant cells have spread to blood or bone marrow.

27. (NEW) The method according to claim 1, wherein the antibodies are MOC31 and BM7, or antigen binding fragments thereof.

28. (NEW) The method according to claim 14, wherein the first immunotoxin comprises a PE molecule conjugated to a MOC31 antibody or an antigen-binding antibody fragment thereof, and the second immunotoxin comprises a PE molecule conjugated to a BM7 antibody or an antigen-binding antibody fragment thereof.